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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,169	04/11/2001	Andrew G. Lee	PC10636ATMC	1529

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
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GROTON, CT 06340

EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
05/05/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	09/833,169	LEE ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-12,40-43,45-48 and 50-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12,40-43,45-48 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/1/08 has been entered.

Claims 10-12, 40-43, 45-48 and 50-55 are under examination by the current Examiner.

Comment: In claims 12 and 48 the chemical name is misspelled. It should be sulfonyl and not "sufonyl". Please correct.

Withdrawn rejections:

Applicant's amendments and arguments filed 2/1/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-43, 46-48 and 50-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutically acceptable salt, N-oxide, ester

and quaternary ammonium salts of the claimed compound estrogen agonist/antagonist compounds, does not reasonably provide enablement for prodrugs of the estrogen agonist/antogonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims without an undue amount of experimentation.

Let the Examiner be clear: Applicant is not enabled for prodrugs.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) Scope or breadth of the claims

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, estrogen agonist/antagonist compounds for use in a method of treating female sexual disorder. However, Applicant is purporting to use any and all prodrugs of the estrogen agonist/antagonist in the method of treating female sexual arousal disorder.

2) Nature of the invention

The nature of the invention is directed to methods of treating female sexual arousal disorder with estrogen agonist/antagonist compounds and a cyclic guanosine monophosphate elevator.

3) Relative level of skill possessed by one of ordinary skill in the art

The relative level of skill possessed by one of ordinary skill in the art of human sexual dysfunction research is relatively high, as a majority of lead investigators directing scientific research and development in this particular technological area possess an MD or Ph.D. in a scientific discipline such as human physiology, organic synthetic chemistry, polymer chemistry, medicinal chemistry, biochemistry, pharmacology, biology or the like.

4) State of, or the amount of knowledge in, the prior art

The art teaches that there is a paucity of physiological and biochemical data pertaining to female genital sexual arousal function due in part to the lack of reliable experimental models and tools for the investigation of female arousal (Abstract: Traish et al. Archives of Sexual Behavior 2002, 31(5), 393-400). Traish et al. teach that female sexual arousal is a complex process which requires integration of signals from various neurotransmitters and vasoactive agents (page 398, future directions).

Ettmayer et al. (J Med Chem 2004, 47(10), 2393-2404) teach on page 2401 that: "the prodrug strategy should only be considered as a last resort" and "At the beginning of each prodrug program, there should be a clear definition of the problem to solve and defect to improve."

5) Level or degree of predictability, or a lack thereof, in the art

Testa (Biochemical Pharmacology 2004; 68, 2097-2106) teaches that in vitro and in vivo behavior of prodrug candidates may differ from that of the parent drug in ways that go beyond the original pharmaceutical, pharmacokinetic or pharmacodynamic objective being pursued (Abstact). On page 2098, Testa discloses that prodrug optimization may be difficult to predict and achieve because of biological variety (1.3. Challenges in prodrug research).

On page 2402, Ettmayer et al. disclose the "inherent difficulties and additional layers of complexity a prodrug strategy might face".

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Applicant teaches how to make various prodrugs on page 59, line 5 through page 60, line 15 but there is no guidance on which ones might work in the invention. There does not appear to be any working examples of a prodrug. Applicant has not disclosed what problem is going to be solved by making the prodrug.

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to a method of treating female sexual arousal disorder. Example 3 on page 65 is prophetic and details how a subjective study might be performed but provides no data.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

MPEP 2164.03 [R-2] states: The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the

predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

In the instant case, one of ordinary skill in the art would have to conduct a myriad number of experiments in an unpredictable art comprising first finding a defect in the drug and a rationale to create a prodrug; chemically synthesizing and purifying the prodrug and testing the prodrug in a clinical setting to see if it is effective. This is especially difficult when the art teaches that there is a lack of reliable experimental models and tools for the investigation of female arousal to begin with. The breadth of the claims includes all of the hundreds of thousands of compounds as well as the presently unknown list of potential prodrug derivatives embraced by the claims. As a result of Applicant's lack of disclosure of prodrugs and the unpredictability in the art of prodrugs, one of ordinary skill in the art would be required to conduct an undue amount of experimentation to figure out which prodrugs might work in the method.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that

may or may not be workable." (Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10-12, 40-43, 45-48 and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaplan et al. (Urology 1999, 53, 481-486) in view of MacLean et al. (EP 0792641) and Miller et al. (US 5,998,402) and Gauthier et al. (J. Med Chem 1997, 40, 2117-2122 filed with IDS on 6/18/06) and with respect to claim 50 Berge et al. (Journal of Pharmaceutical Sciences 1977, 66(1), 1-19) as evidenced by MedlinePlus Medical Encyclopedia: Atrophic vaginitis.

With respect to the scope of enablement rejection above, please note that this rejection only covers the scope for which Applicant is enabled as discussed above.

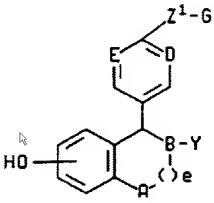
Applicant claims a method for treating female sexual arousal disorder comprising orally administering an effective amount of an estrogen agonist/antagonist and a cyclic guanosine monophosphate elevator.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Kaplan et al. establish *the concept* of treating women with sexual arousal dysfunction with concurrent administration of hormone replacement therapy and sildenafil as explained below. Kaplan et al. teach treating postmenopausal women with sexual dysfunction (the most common symptoms were decreased arousal and decreased lubrication) by oral administration of sildenafil; a cyclic guanosine monophosphate elevator (Abstract and page 482, RESULTS). Kaplan et al. teach that lubrication was increased by 23.2% in the study (Abstract; results and conclusion). Kaplan et al. teach that women treated with hormone replacements had a higher baseline lubrication (page 483, middle left column and page 484, Figure 2 and right column). Kaplan et al. conclude that the use of hormone replacement therapy did not alter the response to sildenafil (page 484, lower right column) and that the overall scores between those taking hormone replacements and those that did not were no different (page 483, left column). Thus, subjects in the study of Kaplan et al. received both sildenafil and compounds used in hormone replacement therapy.

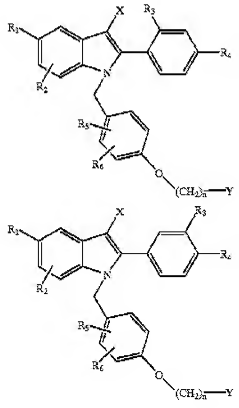
MacLean et al. teach the use of estrogen agonists/antagonists in the treatment of vaginal atrophy (atrophic vaginitis) (Claims 1-3 and 5). MacLean et al. teach compounds of the structure and their salts, N-oxides, ester or quaternary ammonium salts (claim 1):



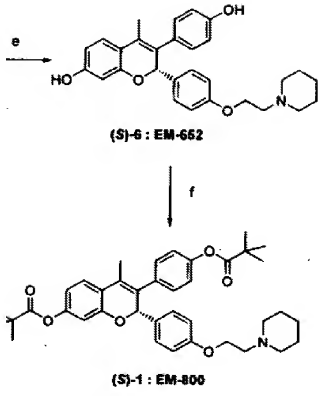
MacLean et al. teach tamoxafin and raloxifene as estrogen agonists (page 2, lines 8-20). Maclean et al teach making hard gelatin capsule and tablets for oral administration (page 19, line 30 and page 20, lines 1-45).

MedlinePlus medical encyclopedia teaches that atrophic vaginitis is characterized by decreased lubrication and caused by a decrease in estrogen (page 1 of 2). Treatment can be done with estrogen replacement therapy (page 1 of 2).

Miller et al. teach compounds of the following structure as estrogenic agents (Abstract and claims 1-107).



Gauthier et al. teach the following compounds as for use in estrogen sensitive diseases (page 2118, scheme 1; page 2119, table 1; and page 2121, summary)



Berge et al. teach tartrate salts as FDA approved commercially marketed salts (page 2, Table 1).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Kaplan et al. is that Kaplan et al. do not expressly teach the instantly claimed estrogen agonists/antagonists and more specifically the tartrate salt in the method of treating postmenopausal female sexual dysfunction with sildenafil or the population of premenopausal women. This deficiency in Kaplan et al. is cured by the teachings of Maclean et al., Miller et al., and Gauthier et al. as evidenced by the MedlinePlus medical encyclopedia.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to orally administer the compounds taught by MacLean et al., Miller et al. and Gauthier et al. in the method of Kaplan et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because: 1) female sexual arousal disorder can be characterized by a decrease in vaginal lubrication (as noted by Applicant on page 6, line 16 of the instant specification); 2) Kaplan et al. teach hormone replacement therapy coupled with sildenafil can increase vaginal lubrication in postmenopausal women; and 3) the art teaches the oral administration of the estrogen agonist/antagonist compounds to treat vaginal atrophy, which is characterized by decreased lubrication and decreased estrogen, and estrogen sensitive disorders as explained above. In the absence of evidence to the contrary, it is the Examiner's position that treatment of vaginal atrophy results in increased vaginal lubrication. The common thread is that both the estrogen agonist/antogonists and sildenafil are associated with increasing vaginal lubrication. One of ordinary skill in the art would have been motivated to combine actives that increase vaginal lubrication in a method of treating female sexual arousal disorder where women suffer from decreased vaginal lubrication with at least an expectation of an additive effect with respect to an increase in vaginal lubrication.

With respect to the limitation of premenopausal women the Examiner notes that there are only two patient populations to treat: pre- and postmenopausal women. Premenopausal are known to suffer from atrophic vaginitis as evidenced by the Medical Encyclopedia. Therefore it

would be obvious to treat premenopausal women as well as postmenopausal women with the instantly claimed combination of actives and expect increased vaginal lubrication. With respect to the tartrate salt limitation, the art teaches tartrate salts and it is merely judicious selection of the salt as taught by Berge et al. by one of ordinary skill in the art in the absence of evidence to the contrary. One of ordinary skill in the art would expect the vaginal lubrication to increase upon administration of the actives and thus treat sexual arousal dysfunction with a reasonable expectation of success.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Examiner, Art Unit 1616